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LETTERS

Iridium-catalysed labelling of anilines, benzylamines and nitrogen heterocycles using deuterium gas and cycloocta-1,5-dienyliridium(I) 1,1,1,5,5,5-hexafluoropentane-2,4-dionate

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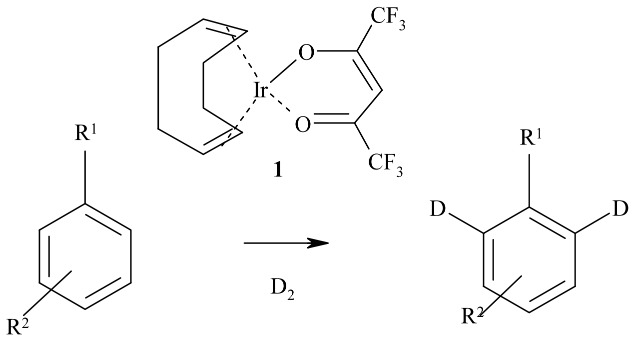
Abstract—A wide range of variously substituted anilines, benzylamines, and nitrogen heterocycles may be conveniently deuterated by exchange with deuterium gas and cycloocta-1,5-dienyliridium(I) 1,1,1,5,5,5-hexafluoropentane-2,4-dionate. The isotopic exchange can be carried out efficiently in dimethylformamide or dimethylacetamide, hence it is directly applicable to the deuteration of polar compounds such as pharmaceuticals. Isotope incorporation is rapid and yields *ortho*-regiospecificity. © 2003 Elsevier Science Ltd. All rights reserved.

The preparation of organic compounds labelled with isotopic hydrogen is of essential importance in the chemical, biological and environmental sciences. Hence numerous methodologies have been developed for the ^{2}H- and ^{3}H-labelling of organic substrates. Possibly the most versatile of these approaches is *ortho*-directed deuteration. The isotope for such *ortho*-exchange procedures may derive from D_2O,[1] T_2O,[2] D_2 gas[3] or T_2 gas.[4] In the former case either $RhCl_3{\cdot}3H_2O$ or Ru-(Acac)$_3$ have been utilised in dipolar aprotic solvents, whilst in the latter case variants of the Crabtree catalyst[5] are utilised, though reactions here are limited to non-polar solvents, typically dichloromethane.

Recently we reported the development of a new range of improved catalysts based upon cycloocta-1,5-dienyliridium(I) acetylacetonate, several of which demonstrate excellent isotopic exchange catalysis with a D_2O donor.[6] We now report that one of these complexes, cycloocta-1,5-dienyliridium(I) 1,1,1,5,5,5-hexafluoropentane-2,4-dionate (**1**), may be used to deuterate compounds using deuterium gas. Moreover with some substrates, particularly benzylamines, anilines and some *N*-heterocycles the activity of this catalyst is maintained even in DMF or dimethylacetamide (Scheme 1). This is particularly useful for pharmaceuticals, agrochemicals and suchlike agents, which are usually polar and insoluble in hydrochlorocarbons. A simple, high-yielding, single-step preparation of the catalyst from a readily available commercial precursor is described.[7]



R¹ = Directing group, R² = Other substituent

Scheme 1.

Keywords: *ortho*-labelling; cycloocta-1,5-dienyliridium(I) 1,1,1,5,5,5-hexafluoropentane-2,4-dionate; deuteration; CH-activation; isotope-exchange; cycloocta-1,5-diene; acetylacetonate; benzylamines; anilines.

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To ascertain the generality of the labelling procedure, **1** was assessed[8] against a panel of substrates chosen to encompass a range of electronic and steric influences. The regiochemistry of labelling was analysed by ^{2}H and/or ^{1}H NMR and the degree of labelling determined by LC–MS. The results are given in Table 1.

Definitive assignment of the labelling regiochemistry by ^{2}H NMR was possible in many cases and the deuterium was shown to be located at positions *ortho* to the directing group. In some cases assignment was precluded by the overlap of NMR resonance positions, compounded by the low spectral dispersion of deuterium.

The catalyst proved effective in labelling all the substrates, recoveries were good and deuteration was observed whether the substrates were electron-rich or poor. Benzylamines could be unsubstituted, mono- or di-substituted at, or α to, nitrogen. The labelling of anilines was particularly facile, either directly with the aniline itself or via the reduction of the corresponding nitro-compound.

Studies of the reaction time-course, with both 4-methoxybenzylamine and 7,8-benzoquinoline, showed that equilibrium was reached within 3–4 h even with sub-stoichiometric quantities of catalyst. Moreover, pre-treatment of the system with hydrogen gas showed no effect upon the labelling efficiency when the hydrogen was subsequently replaced by deuterium. This should significantly reduce radioactive waste when the catalyst is used with tritium.

The catalytic activity observed could be mediated through an iridium dionate hydride species. If so, the precipitation of iridium during the deuteration of some substrates would reflect a low degree of stabilisation by the dionate ligand. Alternatively, in view of the labelling of anilines, which cannot form five-ring cyclometalated intermediates, the reaction may be mediated via precipitated iridium metal or even by an iridium colloid or cluster generated in situ.[9] The continued effectiveness of the catalytic system in the presence of mercury argues against this explanation;[10] however, the iridium precipitate formed during the deuteration of 4-aminobenzoic acid does demonstrate some catalytic activity. Interestingly, the regiochemistry of deuteration for this latter substrate (*ortho* to NH_2) is opposite to that observed when a D_2O donor is used (*ortho* to CO_2H), suggesting different mechanisms for these two reactions. More detailed mechanism studies are ongoing and will be reported elsewhere.

Table 1.

Substrate	Atom% D (No. of atoms)	Regiochemistry
1-(4-Fluorophenyl)ethylamine	66 (2)	[a,b]
1,1-Diphenylmethylamine	50 (4)	[a,b]
1,2-Diphenylethylamine	57 (4)	[c]
4-Iodobenzylamine	42 (2)	[c]
3-Methoxybenzylamine	48 (2)	[a,b]
4-Methoxybenzylamine	55 (2)	[a,b]
4-Methylbenzylamine	69 (2)	[a,b]
Benzylamine	70 (2)	[c]
Biphenyl-2-ylmethylamine	38 (1)	[c]
Biphenyl-3-ylmethylamine	49 (2)	[c]
Naphthalen-2-ylmethylamine	45 (2)	[c]
4-Trifluoromethylbenzylamine	69 (2)	[a,b]
1-Methyl-1-phenylethylamine	60 (2)	[a,b]
N-Methylbenzylamine	94 (2)	[a]
N,*N*-Dimethylbenzylamine	35 (2)	[a]
4-Aminotoluene	77 (2)	[a]
4-Aminobenzoic acid	80 (2)	[a,b]
4-Aminoacetophenone	72 (2)	[a]
2-Phenyl-1*H*-imidazole	34 (2)	[a,b]
2-Phenylpyridine	51 (2)	[a,b]
7,8-Benzoquinoline	36 (1)	[a,b]

[a] Labelling regiochemistry assigned as '*ortho*' from proton NMR and MS.

[b] Labelling regiochemistry assigned as '*ortho*' from deuterium NMR.

[c] Labelling regiochemistry not assigned.

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7. Commercial [di-μ-chlorobis[1,2,5,6-η)-1,5-cyclooctadiene]diiridium (300 mg) was stirred under nitrogen in vacuum degassed ether (6.0 ml) at which point it was only partly dissolved. 1,1,1,5,5,5-Hexafluoro-2,4-pentanedione (300 μl) in ether (0.6 ml) was then added via a syringe and the reaction stirred for 10 min. Sodium hydroxide solution (1 M, 1.25 ml) was then added, dropwise via a syringe. During this phase the remaining crystals of the precursor dissolve and the mixture became a deep claret colour. Water (3.0 ml) was then added, again via a syringe, and the resulting biphasic mixture stirred under nitrogen for a further 10 min. The ether layer was evaporated under a slow stream of nitrogen, leaving clumps of purple crystals in the residual aqueous phase. The aqueous supernatant was decanted and the crystals washed twice more by decantation with 2.0 ml portions of water. Finally, the crystals were filtered and dried overnight over silica gel leaving cycloocta-1,5-dienyliridium(I) 1,1,1,5,5,5-hexafluoropentan-2,4-dionate (412.5 mg, 91%) as a fine free-flowing claret-coloured solid. ^{1}H NMR δ (CDCl$_3$) 1.75 (4H, q, $J=7.5$ Hz), 2.30 (4H, m), 4.31 (4H, s), 6.32 (1H, s) ppm. ^{13}C NMR δ (CDCl$_3$) 31.1, 62.6, 93.1, 118.5 (quartet), 174.3 (quartet) ppm. MS (EI mode) m/z 508/506 a.m.u. Found C, 30.55%; H, 2.91%, req. C, 30.67%; H, 2.95%.
8. A typical deuteration protocol is as follows: The substrate (0.04 mmol) and catalyst (0.01 mmol) were dissolved in DMF or DMA (250 μl) and stirred under deuterium gas for 4 h at room temperature. The labelled substrate was then isolated by a suitable solvent extraction procedure, e.g. for anilines and benzylamines, an ether/hydrochloric acid partition, basification with NaOH solution, extraction into ether and removal of the solvent under a stream of dry nitrogen.
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